



Consommation et  
Affaires commerciales Canada

Consumer and  
Corporate Affairs Canada

Bureau des brevets

Patent Office

Ottawa, Canada  
K1A 0C9

(11) (C) **1,321,754**

(21) 616,401

(22) 1992/07/10

(45) 1993/08/31

(52) 167-276

C.L. CR. 167-164

(51) INTL.CL. <sup>5</sup> A61K-031/135; A61K-009/22

(19) (CA) **CANADIAN PATENT** (12)

(54) **Delivery System**

(72) Baker, Richard W. , U.S.A.  
Brooke, James W. , U.S.A.  
Smith, Kelly L. , U.S.A.

(73) **Wellcome Foundation Limited, (The) , U.K.**

(57) **15 Claims**

**Canada**

CCA 3254 (10-82) 41 7530-21-936-3254

**ABSTRACT**

A composition for use in an aqueous environment, which comprises a formulation containing a water-soluble active ingredient, a semipermeable membrane surrounding the formulation, and particulate water-soluble pore-forming material dispersed within the membrane, whereby, in use in an aqueous environment, the pore-forming material is dissolved forming pores in the semipermeable membrane, the active ingredient is taken up in solution thus creating an osmotic pressure gradient across the membrane between the solution and the aqueous environment, and water from the aqueous environment is diffused through the semipermeable membrane into contact with the active ingredient concurrently while a solution of the active ingredient is discharged through the pores of the membrane into the aqueous environment. The composition has application in the fields of human and veterinary medicine and also in the field of agriculture. The invention is especially concerned with a controlled release composition containing bupropion hydrochloride for sustained release.

The present invention relates to a novel composition which affords a continuous discharge of an active ingredient in a controlled manner, to the preparation of such composition, and to its use in the medical, veterinary and other fields.

10 U.S. patents 3,845,770 and 3,916,899 relate to a composition or device comprising an active ingredient and a semipermeable membrane surrounding the active ingredient and through which is provided a passageway. In use, the composition is contacted with a fluid which permeates or diffuses through the membrane and dissolves the active ingredient. In this way, an osmotic pressure gradient is established across the membrane with the result that the solution of the active ingredient is discharged or released through the passageway into the ambient fluid. U.S. patents 4,160,452 and 4,200,098 relate to similar compositions in which a passageway or portal is also used for the discharge of the solution. All such compositions or devices suffer from the disadvantage that they require the passageway or portal to be formed, for example by drilling, before the composition can be used.

20 U.S. patent 4,016,880 relates to a composition or dispenser in which the semipermeable membrane or wall is provided with sites of structural weakness. As a result of the osmotic pressure gradient that builds up in use, the membrane fractures at the sites of weakness thereby forming passageways in situ, through which the solution is discharged. The disadvantage of this composition is that the discharge of the solution is not readily controllable.

30 J.Pharm.Sci., 1983, 72/7, pages 772 to 775 relates to tablets coated with a polyvinyl chloride membrane in which is dispersed particulate water-soluble pore-forming material. In use, an aqueous liquid dissolves the particulate water-soluble pore-forming material to give a highly porous membrane in situ. The aqueous liquid then gains access through the pores so formed to the tablet within the membrane and dissolves it, the resulting solution discharging out of the membrane through the pores. The disadvantage of this composition is also that the discharge of the solution is not readily controllable.

The present invention seeks to provide a composition which affords a continuous discharge of a solution of an active ingredient in a controlled manner.



The invention seeks to provide a composition that can be manufactured simply and reproducibly without requiring any subsequent manufacturing operation, such as drilling, as is required by a number of the prior art compositions described above.

Accordingly, the present invention provides, in one aspect, a composition for use in an aqueous environment, which comprises a formulation containing a water-soluble active ingredient, a semipermeable membrane surrounding the formulation, and particulate water-soluble pore-forming material dispersed within the membrane, whereby, in use in an aqueous environment, the pore-forming material is dissolved forming pores in the semipermeable membrane, the active ingredient is taken up in solution thus creating an osmotic pressure gradient across the membrane between the solution and the aqueous environment, and water from the aqueous environment is diffused through the semipermeable membrane into contact with the active ingredient concurrently while a solution of the active ingredient is discharged through the pores of the membrane into the aqueous environment.

The formulation suitably includes a water-soluble osmotic enhancing agent in an amount, by weight, equal to or greater than the weight of the active ingredient.

Suitably an agent to increase the water permeability is included in the composition, for example, polyethylene glycol.

The invention is especially concerned with a controlled release composition containing bupropion hydrochloride for sustained release.

Examples of the formulation containing a water-soluble active ingredient include a compressed form of the active ingredient optionally in admixture with one or more excipients, and a prill seed, as defined hereinafter, having a coating of a water-permeable polymer, in which seed or coating or both the active ingredient is dispersed. In the former case, the compressed form is, preferably, a tablet or a pill and preferred examples of an excipient include an osmotic enhancing agent and standard formulating excipients, such as a filler and a binding agent. Such tablet or pill forms are prepared in accordance with standard techniques known in the art of pharmacy.

- 10 As used herein, the prill seed of use with the polymer-coated prill seeds described above are solid particles, the largest dimension of which is from 0.1 to 4.0mm, usually from 0.2 to 0.3mm. They are normally substantially spherical in shape but may be ovoidal or even of irregular shape, and they are generally used in capsule dosage forms. Preferred examples of prill seeds include those produced from sugar such as sucrose and mannitol, starch, salt such as sodium chloride, and wax. If the active ingredient has a high water solubility, then the prill seed may have a low water solubility or indeed may even be insoluble in water. If, on the other hand, the active ingredient has a low water solubility, then it is preferred that the prill seed has a high water solubility so as to
- 20 increase the osmotic pressure within the composition during its use in an aqueous

environment. The preparation of such prill seeds may be carried out in accordance with standard techniques known in the art of pharmacy.

Alternatively, a number of different types of prill seeds are commercially available from, for example, Ingredient Technology Corporation, Pennsauken, New Jersey, U.S.A.

10 The water-permeable polymer coating of use with the polymer-coated prill seeds described above may be the same polymeric material as is described hereinafter in relation to the semipermeable membrane but is, preferably, a polymeric material having a higher permeability to water. Examples of such latter material include cellulose acetate. It is also preferred that the active ingredient is dispersed within the polymeric material rather than within the prill seed. In such circumstances, from 0.5 to 5.0 parts of active ingredient on a weight basis are normally used for every one part of polymer.

The polymer-coated prill seeds may be prepared by standard techniques known in the art of pharmacy. For example, the prill seeds may be coated with a solution of the polymer optionally containing (also in solution but, if not, then in suspension) the active ingredient. Such coating is usually carried out on a fluidized bed coater in which the coating solution is sprayed into the suspending air stream thereby coating the prill seeds.

20 A composition, wherein the formulation is a polymer-coated prill seed, as described herein, has a number of advantages over the corresponding composition, wherein the formulation is a compressed form, for example a tablet or pill. A given dosage of the former composition, for example, has a much greater surface area than the equivalent dosage of the latter composition and this may, therefore, be of advantage in relation to active ingredients with low water solubility in that the greater surface area of the composition allows for more of the active ingredient to be dissolved and at a faster rate.

30 Examples of water-soluble active ingredients of use with the composition of the present invention include water-soluble active ingredients used in the fields of human and veterinary medicine and of agriculture, such as nutrients, pesticides, fungicides, herbicides, algicides, vitamins, fertilizers and soil trace minerals or elements. Particular examples of such active ingredients include d-pseudoephedrine hydrochloride, bupropion hydrochloride, soluble potassium salts such as

1321754

potassium chloride, potassium citrate, potassium gluconate, chlorpheniramine maleate, propranolol hydrochloride, cimetidine, phenylpropanolamine hydrochloride, dextromethorphan hydrobromide, ascorbic acid, aspirin, acetaminophen, codeine salts, methomyl, copper sulfate and ammonium nitrate.

As used herein, an osmotic enhancing agent is a substance having a high molar water solubility and which is capable of achieving, in use of the composition of the present invention in an aqueous environment, an increase in the osmotic pressure within the composition relative to the osmotic pressure of the aqueous environment. Examples of an osmotic enhancing agent include sugar such as sucrose, lactose, fructose and mannitol, and salt such as sodium chloride, potassium chloride and sodium carbonate.

As used herein, a semipermeable membrane is a membrane that is permeable to water but not permeable to the active ingredient or any osmotic enhancing agent that may be present. The membrane should not be detrimental to the active ingredient and should be suitable for the use to which the composition is intended to be put. The thickness of the membrane is generally from 10 to 500um, preferably from 25 to 50um. The membrane may be made of any material that is suitable for use in reverse osmosis or has application in dialysis. General examples of such material include cellulose esters such as mono-, di- and triacylates including mixed esters, cellulose ethers such as ethyl cellulose, nylons, polycarbonates, poly(dialkylsiloxanes), poly(methacrylic acid) esters, poly(acrylic acid) esters, poly(phenylene oxides), poly(vinyl alcohols), aromatic nitrogen-containing polymers, polymeric epoxides and regenerated cellulose. Specific examples include cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate propionate, cellulose tripropionate, ethyl cellulose and nylon 6.

The semipermeable membrane may optionally contain one or more additives, such as a plasticizer and a water permeability-modifying agent. The plasticizer is, preferably, a non-migrating plasticizer, general examples of which include esters such as a phthalate, phosphate, citrate, adipate, tartrate, sebacate, succinate, glycolate, glycerolate, benzoate and myristate esters and sulfonamides. Specific examples include dimethyl phthalate, dipropyl phthalate, di-(2-ethylhexyl)phthalate, tributyl phosphate, triacetyl phosphate, and tributyl citrate.

As used herein, a water permeability-modifying agent is a material which is capable of enhancing the permeability of water through the semipermeable membrane. General examples of such a material include the poly(alkylene glycols), esters and polyesters of poly(alkylene glycols), polyhydric alcohols and esters and polyesters of polyhydric alcohols. Specific examples include poly(ethylene glycols) 300, 400, 600, 1500 and 1540, poly(propylene glycol), 1,3-butylene glycol, glycerine, ethylene glycol dipropionate and ethylene glycol butyrate.

The particulate water-soluble pore-forming material of use in the composition of the present invention, preferably, has a maximum particle size not exceeding 500um in its longest dimension and has an average particle size from 5 to 100um. The material is, preferably, also insoluble in the organic solvent in which the polymeric material is dissolved for forming the semipermeable membrane as described hereinafter. Examples of water soluble pore-forming material include water-soluble sugars such as lactose, sucrose, sorbitol and mannitol, and salts such as sodium carbonate, sodium chloride, calcium chloride, potassium chloride and sodium sulphate.

The present invention also provides a process for the preparation of a composition, as defined herein, which comprises coating a formulation containing a water-soluble active ingredient with a coating mix containing in an organic solvent a solution of a material for forming a semipermeable membrane that surrounds the formulation and a suspension of particulate water-soluble pore-forming material for dispersion within the membrane, and drying the coated formulation.

The coating operation may be carried out by spraying the coating mix on to the formulation in, for example, a rotating pan coater or fluidized bed coater. The drying operation is carried out conventionally.

As mentioned previously, it is preferred that the particulate water-soluble pore-forming material is insoluble in the organic solvent. If, however, it is not, then a suspension of the material may be obtained by suspending it in a solvent in which it is insoluble, and then coating the formulation separately but simultaneously with the solution and the suspension.

Examples of an organic solvent include acetone.



As mentioned previously, the composition of the present invention may be used in the human and veterinary and other fields. In fact, it may be used in any field where there is need for controlled discharge of a water-soluble active ingredient from a composition. Thus, it is believed that the composition may be of use in the field of agriculture for, for example, the controlled discharge of water-soluble fertilizers, soil trace minerals, or elements, fungicides or herbicides. The primary application of the composition, however, is in human and veterinary medicine.

If the composition of the present invention is intended for use in human and/or veterinary medicine, then the composition and its components should, preferably, be pharmaceutically acceptable. Oral pharmaceutical compositions are preferred especially where the formulation used with the composition is a tablet or pill or is a water-soluble polymer coated prill seed as herein defined. Thus, the most preferred pharmaceutical compositions are tablets or pills or are capsules containing prill seed compositions.

The present invention will now be further described with reference to drawings and examples, neither of which should be construed as limiting the invention in any way.

In the drawings which are not drawn to scale, Figures 1A and 1B are plan views of a composition of the invention in which the formulation is a tablet (1A) or a polymer-coated prill seed (1B);

Figures 2A and 2B are sectional views taken along the line X-X in a horizontal direction and illustrating the structures of the compositions before their use in an aqueous environment;

Figures 3A and 3B are the same views as depicted in Figures 2A and 2B respectively but illustrating the structures of the compositions after the pore-forming material has been dissolved.

Referring to the Figures, there are shown compositions 10 comprising a tablet 14 containing a water-soluble active ingredient (in Figures 1A, 2A and 3A), or a polymer-coated prill seed 14, the polymer-coating 16 containing a water-soluble active ingredient (in Figures 1B, 2B and 3B), a semipermeable membrane 11, and particulate water-soluble pore-forming material 12 and 13 dispersed within the membrane 11. In the majority of places, the pore-forming material 12 is

1321754

- 8 -

aggregated together across the thickness of the membrane 11 whilst in a few places the material 13 is not so aggregated. The polymer coated prill seed in Figures 1B, 2B and 3B comprises the coating 16 on seed core 17.

In use of the composition 10 in an aqueous environment (not shown), the pore-forming material 12 that is aggregated together across the thickness of the membrane 11 is dissolved in water from the aqueous environment thus forming pores 15 in the membrane 11. Some of the water-soluble active ingredient within the tablet 14 (in Figures 1A, 2A and 3A) or within the polymer coating (in  
10 Figures 1B, 2B and 3B) in the immediate vicinity of the pores 15 then comes into contact with water and is taken up in solution thus setting up an osmotic pressure gradient across the membrane 11 between the aqueous solution of the active ingredient and the aqueous environment. The effect of the pressure gradient so created is that water from the aqueous environment diffuses or permeates through the membrane 11 into contact with the active ingredient while an aqueous solution of the active ingredient is discharged through the pores 15 of the membrane 11 into the aqueous environment and this process continues until the concentration of the solution of the active ingredient within the  
20 membrane 11 is substantially the same as that outside the membrane 11 in the aqueous environment at which point there is no longer any osmotic pressure gradient between the two solutions, the bulk of the active ingredient having been discharged as an aqueous solution from the composition 10 into the aqueous environment.

EXAMPLE 1

Tablets containing 100mg bupropion hydrochloride and 500mg lactose were prepared using a conventional tablet press. Fifty tablets were placed in a miniature pan coater. A polymer solution was prepared by dissolving cellulose acetate (CA 383-40 from Eastman Chemical Products, Inc., Kingsport, Tenn.) and poly(ethylene glycol) (Polyglycol E-400 from Dow Chemical Co., Midland, Mich.) in acetone and adding impalpable lactose (particle size: 2-20 $\mu$ m) to give a mixture containing cellulose acetate: poly(ethylene glycol): lactose in the weight % ratio of 40:40:20 and a total solids content of 50g/L. The polymer mixture was sprayed onto the tablets in the pan coater to give membrane-coated tablets in which the membrane coating weighs 27 mg, when dried.

Drug release rates were determined for the tablet compositions by placing them in simulated gastric buffer (pH 1.5) at 37°C and periodically measuring the bupropion hydrochloride concentration in the buffer. After 2 hr., about 45% of the bupropion hydrochloride was released; after 4 hr., about 70%; and after 6 hr., about 90%.

EXAMPLE 2

Tablets containing 100mg bupropion hydrochloride and 500mg lactose were prepared using a conventional tablet press. Fifty tablets were placed in a miniature pan coater. A polymer solution was prepared by dissolving cellulose acetate (CA 383-40) and poly(ethylene glycol) (Polyglycol E-400) in acetone and adding impalpable lactose to give a mixture containing cellulose acetate: poly(ethylene glycol): lactose in the weight % ratio of 67:13:20 and a total solids content of 50g/L. The polymer mixture was sprayed onto the tablets in the pan coater to give membrane-coated tablets in which the membrane coating weighs 35 mg, when dried.

Drug release rates were determined for the tablet compositions by placing them in simulated gastric buffer (pH 1.5) at 37°C and periodically measuring the bupropion hydrochloride concentration of the buffer. After 2 hr., about 10% of the bupropion hydrochloride was released; after 4 hr., about 25%; after 6 hr., about 40%; and after 8 hr., about 55%.

EXAMPLE 3

Tablets containing 120g d-pseudoephedrine hydrochloride, 5mg triprolidine hydrochloride, 125mg lactose, and 28mg starch were prepared using a conventional tablet press. Fifty tablets were placed in a miniature pan coater. A polymer solution was prepared by dissolving cellulose acetate (CA 398-10 from Eastman Chemical Products, Inc., Kingsport, Tenn.) and poly(ethylene glycol) (Polyglycol E-400) in acetone and adding powdered sodium carbonate (particle size: 30-200um) to give a mixture containing cellulose acetate: poly(ethylene glycol): sodium carbonate in the weight % ratio of 4:40:20 and a total solids content of 50g/L. The polymer mixture was sprayed onto the tablets in the pan coater to give membrane-coated tablets in which the membrane coating weighs 64 mg, when dried.

Drug release rates were determined for the tablet compositions by placing them in simulated gastric buffer (pH 1.5) and 37°C and periodically measuring the drug concentration. After 1 hr., about 33% of the d-pseudoephedrine hydrochloride and 32% of the triprolidine hydrochloride was released; after 2 hr., about 53% of each drug was released; after 3 hr., about 71% and 74%, respectively; and after 4 hr., about 97% and 85%, respectively.

EXAMPLE 4

A total of 40g of sucrose/starch prill seeds (Nu-Pareil 20/25 mesh prills from Ingredient Technology Corp., Pennsauken, N.J.) was placed in a cylindrical bed (16 in. long x 1.5 in. diameter) and fluidized with dry compressed air at 30 psi. The prills were then coated with a solution of 12g of cellulose acetate (CA 398-10 from Eastman Chemical Products, Inc., Kingsport, Tenn.) and d-pseudoephedrine hydrochloride (36g) in ethanol (200ml) and dichloromethane (400ml) using an air brush at 30 psi. Agglomeration was avoided by intermittent application with partial drying. The polymer-coated prills were removed from the bed and allowed to dry for two hours. They were then returned to the fluidized bed and coated with a solution of 7g of cellulose acetate (CA 398-10) and 1g of poly(ethylene glycol) (Polyglycol E-400 from Dow Chemical Co., Midland, Michigan) in 240ml of acetone containing 2g of powdered sodium carbonate (particle size: 30-200um) in suspension. The prill seed compositions thus formed were then allowed to dry.

Drug release rates were determined for the prill seed compositions by placing them in sodium chloride solutions of different concentrations at 37°C to vary the osmotic pressure driving force for drug release, and periodically measuring the d-pseudoephedrine hydrochloride concentration. When the sodium chloride concentration was 0%, the drug release rate was 90mg/hr.; when it was 5%, the release rate was 75mg/hr.; when it was 10%, the release rate was 45mg/hr.; and when it was 20%, the release rate was 10mg/hr.

#### EXAMPLE 5

Sucrose seed prills (Nu-Pareil) were coated with an aspirin (75%)-CA-398-10 (25%) mixture essentially following the procedure of Example 4 but using acetone (containing 10% by weight of total solids) instead of ethanol-dichloromethane. The polymer-coated prill seeds were dried and then overcoated with a 40:40:20 mixture of cellulose acetate (C-398-40 from Eastman Chemical Products, Inc., Kingsport, Tenn.); Polyglycol E-400; impalpable lactose (particle size: 5-20um) in acetone (5% by weight total solids). The prill seed compositions thus formed were then allowed to dry.

Drug release rates were determined as in Example 4. After 2 hr. about 60% of the aspirin had been released; after 4 hr. about 80% had been released; and after 8 hr. about 90% had been released.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A controlled release composition for oral administration comprising bupropion hydrochloride in solid sustained release pharmaceutical carrier, said composition releasing about 10% to 45% of bupropion hydrochloride within two hours, releasing about 25% to 70% of bupropion hydrochloride within four hours, and releasing about 40% to 90% of bupropion hydrochloride within six hours, as measured in simulated gastric buffer with a pH of 1.5 to 37°C.

2. A controlled release composition for oral administration comprising bupropion hydrochloride in a solid sustained release pharmaceutical carrier, said composition releasing no more than about 45% of the bupropion hydrochloride within two hours, and releasing more than about 70% within four hours, as measured in simulated gastric buffer with a pH of 1.5 at 37°C.

3. A controlled release composition for oral administration comprising bupropion hydrochloride in a solid sustained release pharmaceutical carrier, said composition releasing no more than about 45% of the bupropion hydrochloride within two hours, and releasing more than about 90% within six hours, as measured in simulated gastric buffer with a pH of 1.5 at 37°C.

4. A controlled release composition for oral administration comprising bupropion hydrochloride as an active ingredient, in solid sustained release pharmaceutical carrier, said composition releasing no more than about 25% of the active ingredient within

13

1321754

four hours and releasing more than about 55% of the active ingredient within 8 hours, as measured in simulated gastric buffer with a pH of 1.5 at 37°C.

5. A controlled release composition for oral administration comprising bupropion hydrochloride as an active ingredient, in solid sustained release pharmaceutical carrier, said composition releasing no more than about 40% of the active ingredient within six hours and releasing more than about 55% of the active ingredient within 8 hours, as measured in simulated gastric buffer with a pH of 1.5 at 37°C.

6. A controlled release composition for oral administration comprising bupropion hydrochloride as an active ingredient, in solid sustained release pharmaceutical carrier, said composition releasing no more than about 45% of the active ingredient within two hours and releasing more than about 50% of the active ingredient within 8 hours, as measured in simulated gastric buffer with a pH of 1.5 at 37°C.

7. A pharmaceutical composition adapted for oral administration comprising bupropion hydrochloride as active ingredient characterized in that the active ingredient is formulated with a solid pharmaceutical carrier which affords a continuous release of active ingredient in a controlled manner.

8. A pharmaceutical composition as claimed in claim 7 characterized in that at least about 10% of the active ingredient is released over a period of 2 hours in simulated gastric buffer.

9. A pharmaceutical composition as claimed in claim 7 or 8 characterized in that at least about 25%

14

1321754

of the active ingredient is released over a period of 4 hours in simulated gastric buffer.

10. A pharmaceutical composition as claimed in claim 7 or 8 characterized in that at least about 40% of the active ingredient is released over a period of 6 hours in simulated gastric buffer.

11. A pharmaceutical composition as claimed in claim 9 characterized in that at least about 40% of the active ingredient is released over a period of 6 hours in simulated gastric buffer.

12. A pharmaceutical composition as claimed in claim 7 characterized in that from about 10% to about 45% of the active ingredient is released over a period of 2 hours in simulated gastric buffer.

13. A pharmaceutical composition as claimed in claim 7 or 12 characterized in that from about 25% to about 70% of the active ingredient is released over a period of 4 hours in simulated gastric buffer.

14. A pharmaceutical composition as claimed in claim 7 or 12 characterized in that from about 40% to about 90% of the active ingredient is released over a period of 6 hours in simulated gastric buffer.

15. A pharmaceutical composition as claimed in claim 13 characterized in that from about 40% to about 90% of the active ingredient is released over a period of 6 hours in simulated gastric buffer.





1321754

2/1

FIG. 1A.

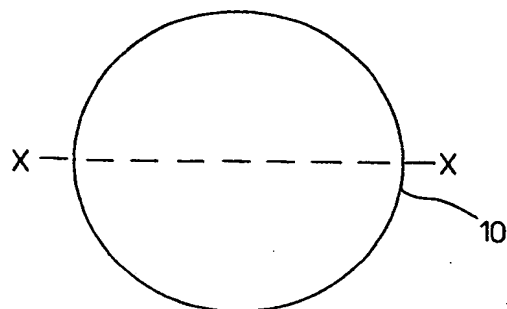


FIG. 2A.

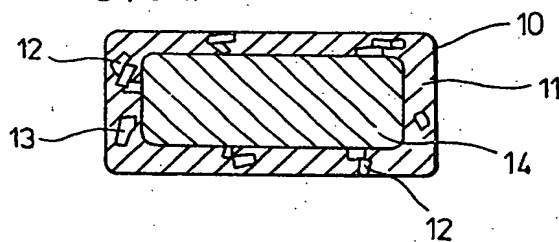
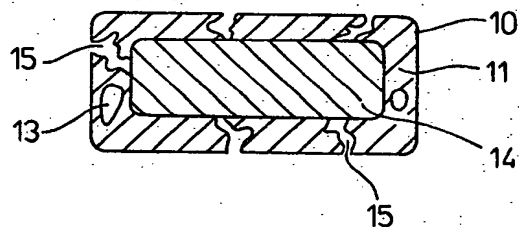


FIG. 3A.



PATENT AGENTS

*Dwight Ogilvy Kierulff*

1321754

2/2

FIG. 1B.

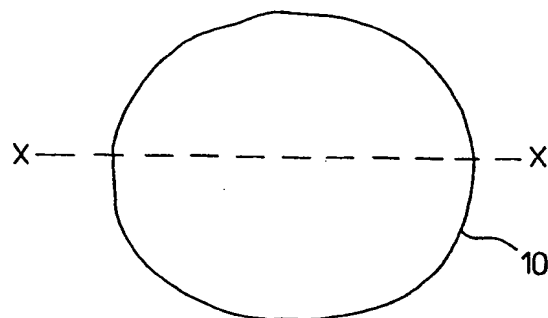


FIG. 2B.

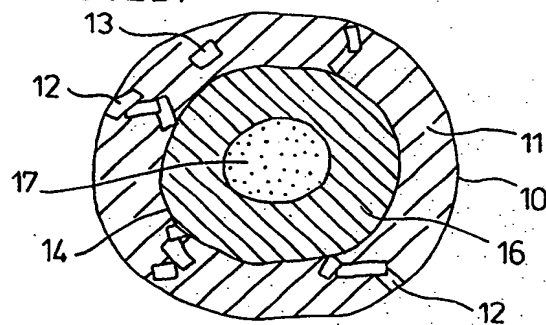
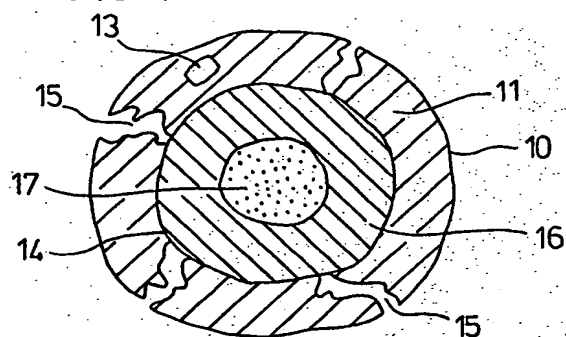


FIG. 3B.



PATENT AGENTS

*Awabey Ogilvy Renault*